



Docket No.: 62138US(49949)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: E. Colli

Application No.: 10/573,164

Confirmation No.: 6611

Filed: November 9, 2006

Art Unit: 1612

For: METHODS FOR TREATING BLADDER
DYSFUNCTION

Examiner: S. N. Qazi

DECLARATION OF LUCIANO ADORINI UNDER 37 C.F.R. §1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Luciano Adorini, MD declare the following:

1. I am presently Chief Scientific Officer at Intercept Pharmaceuticals in Corciano (Perugia), Italy. My *Curriculum Vitae* is attached as Appendix A.

2. I am an expert in the biochemistry of Vitamin D compounds in the treatment of a variety of disorders.

3. I have read and am familiar with the contents of the specification of U.S. Patent Application Serial No. 10/573,164 ("the '164 application), as well as the claims of that application, which provide methods of preventing or treating overactive bladder in a patient comprising administering to a patient a effective amount of a Vitamin D₃ compound.

4. I have read and am familiar with the Office Action dated September 10, 2008 in which the claims of the '164 application are rejected as obvious over: Batcho (US 5,939,408), Bishop, *et al.* WO 98/29123 ("Bishop I") and Bishop, *et al.* US 6,566,353 ("Bishop II") ("the first rejection"); and Batcho (US 5,939,408), in view of Crescioli (J. Clinical Endocrinology & Metabolism) ("the second rejection").

5. With regard to the first rejection, I understand that it is the position of the Patent Office that: Batcho teaches the use of 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol to treat neoplastic disease; Bishop I teaches methods of treating prostatic disease, including prostate cancer and prostate hyperplasia, using vitamin D compounds; Bishop II teaches methods of treating hypercalcemia associated with malignant or neoplastic cells using a vitamin D compound; and it would have been obvious to one of ordinary skill in the art to use 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol to treat overactive bladder, upon a reading of all three references in combination.

6. With regard to the second rejection, I understand that it is the position of the Patent Office that: Batcho teaches 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol and its use to treat neoplastic disease; Crescioli teaches a vitamin D compound to treat BPH; and it would have been obvious to one of ordinary skill in the art to select the compound of Batcho to use in the method of treating BPH as disclosed in Crescioli.

7. I have read Batcho, Bishop I, Bishop II and Crescioli and do not find any indication or suggestion that Vitamin D compounds could be used to prevent or treat overactive bladder.

8. By definition, prostatic disorders such as prostate cancer and prostatic hyperplasia are necessarily related to the prostate gland and are characterized by

abnormal cell proliferation that causes an enlarged prostate gland (hence a disorder that affects only men), which can cause problems of urinating due to squeezing or partial blocking of the urethra.

9. BPH (benign prostatic hyperplasia) is characterized by an enlarged prostate gland (hence a disorder that affects only men), which can cause mild to moderate problems of urinating due to squeezing or partial blocking of the urethra.

10. In contrast, overactive bladder is a disorder characterized by dysfunction of the bladder detrusor muscle and, therefore, affects men and women. The urinating problems associated with overactive bladder, which include urinary urgency, frequency and nocturia, are caused by repeated and uncontrolled contractions of the bladder detrusor muscle.

11. Notwithstanding the similarity in lower urinary tract symptoms between prostatic disorders (*e.g.*, prostate cancer, prostate hyperplasia and BPH) and overactive bladder, the disorders are distinct because the underlying causes and associated mechanisms are distinct and because prostatic disorders only affect men whereas overactive bladder affects both men and women. The disorders involve different target cells and have a different pathogenesis. For example, BPH is considered an inflammatory disease leading to abnormal prostate cell proliferation whereas overactive bladder is primarily a muscular contractile dysfunction.

12. Given the vast differences between prostatic disorders (*e.g.*, prostate cancer, prostate hyperplasia and BPH) and overactive bladder, the claimed methods for preventing or treating overactive bladder would not be obvious in view of Batcho, Bishop I, Bishop II and/or Crescioli and it is unexpected and surprising that Vitamin D₃ compounds could be used to prevent or treat overactive bladder.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application for the patent identified above.

Date: August 4, 2009

Signed: *Luciano Adorini*
LUCIANO ADORINI, M.D.

APPENDIX A

Curriculum Vitae Luciano Adorini, MD

NAME		POSITION TITLE	
ADORINI, Luciano, M.D. Born in Udine (Italy), 27-8-1949, Italian		Chief Scientific Officer	
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Medical School of Padova University, Italy Post-doctoral fellow, UCLA	M.D.	1974 1976-1979	Medical Pathology Immunoregulation

Luciano Adorini, M.D., has conducted postdoctoral studies at the University of California at Los Angeles under the supervision of Prof. Eli Sercarz. He has then directed a research unit at the Preclinical Research Center, Sandoz Pharma Ltd., Basel and has been Associate Director of Roche Milano Ricerche, Milano. He has been Chief Scientific Officer at BioXell in Milano, a spin-off of Hoffmann-La Roche of which he was a co-founder. He is presently Chief Scientific Officer at Intercept Pharmaceuticals, a US privately held biotech. He has been (2005-2008) President of the Italian Society of Immunology, Clinical Immunology and Allergology. He is President of the 15th International Congress of Immunology (Rome 2013).

Dr. Adorini has studied several aspects of antigen recognition by T cells and has analyzed immunoregulatory mechanisms to develop immunosuppressive strategies applicable to the treatment of inflammatory and autoimmune diseases. He has made significant contributions in the field of antigen presentation, peptide-MHC interactions and in the use of synthetic peptides to selectively modulate immune responses in vivo. His current interests are focused on the role of nuclear receptor agonists in immunoregulation, and on the pathogenesis and treatment of autoimmune diseases. His preclinical research work has been clinically translated in a number of different indications. He is author of about 250 scientific publications and is a highly cited researcher in Immunology.

A. Positions and Honors

Positions and Employment

Oct. 74-Sept. 76: Associate scientist at CNEN-Euratom Immunogenetics Group, C.S.N. Casaccia, Rome, Italy.

Sept. 76-Apr. 79: Post-doctoral Fellow of the Cancer Research Institute at the Dept. of Microbiology, University of California, Los Angeles, CA.
Sept. 79-July 88: Researcher at ENEA-Euratom Immunogenetics Group, C.R.E. Casaccia, Roma, Italy.
Feb. 80-Mar. 80: ICRETT Fellow of the International Union against Cancer at the Dept. of Microbiology, University of California, Los Angeles, CA.
Dec. 82-June 83: Visiting scientist at the Dept. of Biology, Massachusetts Institute of Technology, Cambridge, MA.
Oct. 86-July 88: Visiting scientist at the Preclinical Research Center, Sandoz Pharma Ltd., Basel, Switzerland.
Aug. 88-Dec. 92: Laboratory Head, Dept. of Immunology, Preclinical Research, Sandoz Pharma Ltd., Basel, Switzerland
Jan. 93-Dec. 01: Associate Director, Roche Milano Ricerche, Milano, Italy
Jan. 02-Dec. 07: Chief Scientific Officer, BioXell, Milano, Italy
Jan. 08-present: Chief Scientific Officer, Intercept Pharmaceuticals

Other Experience and Professional Memberships

1976-present Member, Italian Society of Immunology
1982-present Member, British Society for Immunology
1984-1987 Steering Committee member, Italian Society of Immunology
1995-present Editorial board member, Chemical Immunology
1997-present Editorial board member, Cellular Immunology
1999-present Editorial board member, Tissue Antigens
2002-present Editorial board member, Human Immunology
2003-present Editorial board member, Immunology Letters
2003-present Editorial board member, The Journal of Immunology
2003-present Member, American Society for Immunology
2002-2005 Vice-President Italian Society of Immunology, Clinical Immunology and Allergology
2005-2008 President Italian Society of Immunology, Clinical Immunology and Allergology
2006 Member NIH study section Cell and Molecular Immunology-A
2009 President-elect Italian Federation of Immunological Societies

Honors

1977-1978 Cancer Research Institute fellowship
1980 ICRETT Fellowship of the International Union against Cancer
2006 Highly cited scientist Immunology (ISI)
<http://hcr3.isiknowledge.com/author.cgi?&link1=Search&link2=Search%20Results&AuthLastName=adorini&AuthFirstName=&AuthMiddleName=&AuthMailInstName=&CountryID=-1&DisciplineID=0&id=5699>

B. Peer-reviewed publications (in reverse chronological order)

1. Tang, J., R. Zhou, D. Luger, W. Zhu, P. B. Silver, R. S. Grajewski, S. B. Su, C. C. Chan, L. Adorini, and R. R. Caspi. 2009. Calcitriol suppresses antiretinal

- autoimmunity through inhibitory effects on the Th17 effector response. *J Immunol* 182: 4624-4632.
2. Sottili, M., L. Cosmi, E. Borgogni, E. Sarchielli, L. Maggi, M. Francalanci, G. B. Vannelli, E. Ronconi, L. Adorini, F. Annunziato, P. Romagnani, M. Serio, and C. Crescioli. 2009. Immunomodulatory effects of BXL-01-0029, a less hypercalcemic vitamin D analogue, in human cardiomyocytes and T cells. *Exp Cell Res* 315: 264-273.
 3. Penna, G., B. Fibbi, S. Amuchastegui, C. Cossetti, F. Aquilano, G. Laverny, M. Gacci, C. Crescioli, M. Maggi, and L. Adorini. 2009. Human benign prostatic hyperplasia stromal cells as inducers and targets of chronic immuno-mediated inflammation. *J Immunol* 182: 4056-4064.
 4. Penna, G., B. Fibbi, S. Amuchastegui, E. Corsiero, G. Laverny, E. Silvestrini, A. Chavalmane, A. Morelli, E. Sarchielli, G. B. Vannelli, M. Gacci, E. Colli, M. Maggi, and L. Adorini. 2009. The vitamin D receptor agonist elocalcitol inhibits IL-8-dependent benign prostatic hyperplasia stromal cell proliferation and inflammatory response by targeting the RhoA/Rho kinase and NF-kappaB pathways. *Prostate* 69: 480-493.
 5. Laverny, G., G. Penna, M. Uskokovic, S. Marczak, H. Maehr, P. Jankowski, C. Ceailles, P. Vouros, B. Smith, M. Robinson, G. S. Reddy, and L. Adorini. 2009. Synthesis and anti-inflammatory properties of 1alpha,25-dihydroxy-16-ene-20-cyclopropyl-24-oxo-vitamin D3, a hypocalcemic, stable metabolite of 1alpha,25-dihydroxy-16-ene-20-cyclopropyl-vitamin D3. *J Med Chem* 52: 2204-2213.
 6. Adorini, L., and G. Penna. 2009. Induction of tolerogenic dendritic cells by vitamin D receptor agonists. *Handb Exp Pharmacol*: 251-273.
 7. Morelli, A., R. Squecco, P. Failli, S. Filippi, L. Vignozzi, A. K. Chavalmane, B. Fibbi, R. Mancina, G. Luciani, M. Gacci, E. Colli, F. Francini, L. Adorini, and M. Maggi. 2008. The vitamin D receptor agonist elocalcitol upregulates L-type calcium channel activity in human and rat bladder. *Am J Physiol Cell Physiol* 294: C1206-1214.
 8. Lee, H. J., S. Paul, N. Atalla, P. E. Thomas, X. Lin, I. Yang, B. Buckley, G. Lu, X. Zheng, Y. R. Lou, A. H. Conney, H. Maehr, L. Adorini, M. Uskokovic, and N. Suh. 2008. Gemini vitamin D analogues inhibit estrogen receptor-positive and estrogen receptor-negative mammary tumorigenesis without hypercalcemic toxicity. *Cancer Prev Res (Phila Pa)* 1: 476-484.
 9. Fibbi, B., A. Morelli, M. Marini, X. H. Zhang, R. Mancina, L. Vignozzi, S. Filippi, A. Chavalmane, E. Silvestrini, E. Colli, L. Adorini, G. B. Vannelli, and M. Maggi. 2008. Atorvastatin but not elocalcitol increases sildenafil responsiveness in spontaneously hypertensive rats by regulating the RhoA/ROCK pathway. *J Androl* 29: 70-84.
 10. Borgogni, E., E. Sarchielli, M. Sottili, V. Santarlaschi, L. Cosmi, S. Gelmini, A. Lombardi, G. Cantini, G. Perigli, M. Luconi, G. B. Vannelli, F. Annunziato, L. Adorini, M. Serio, and C. Crescioli. 2008. Ellocalcitol inhibits inflammatory responses in human thyroid cells and T cells. *Endocrinology* 149: 3626-3634.
 11. Adorini, L., and G. Penna. 2008. Control of autoimmune diseases by the vitamin D endocrine system. *Nat Clin Pract Rheumatol* 4: 404-412.

12. Spina, C. S., L. Ton, M. Yao, H. Maehr, M. M. Wolfe, M. Uskokovic, L. Adorini, and M. F. Holick. 2007. Selective vitamin D receptor modulators and their effects on colorectal tumor growth. *J Steroid Biochem Mol Biol* 103: 757-762.
13. Penna, G., N. Mondaini, S. Amuchastegui, S. Degli Innocenti, M. Carini, G. Giubilei, B. Fibbi, E. Colli, M. Maggi, and L. Adorini. 2007. Seminal plasma cytokines and chemokines in prostate inflammation: interleukin 8 as a predictive biomarker in chronic prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia. *Eur Urol* 51: 524-533; discussion 533.
14. Penna, G., S. Amuchastegui, G. Laverny, and L. Adorini. 2007. Vitamin D receptor agonists in the treatment of autoimmune diseases: selective targeting of myeloid but not plasmacytoid dendritic cells. *J Bone Miner Res* 22 Suppl 2: V69-73.
15. Penna, G., S. Amuchastegui, N. Giarratana, K. C. Daniel, M. Vulcano, S. Sozzani, and L. Adorini. 2007. 1,25-Dihydroxyvitamin D3 selectively modulates tolerogenic properties in myeloid but not plasmacytoid dendritic cells. *J Immunol* 178: 145-153.
16. Penna, G., S. Amuchastegui, C. Cossetti, F. Aquilano, R. Mariani, N. Giarratana, E. De Carli, B. Fibbi, and L. Adorini. 2007. Spontaneous and prostatic steroid binding protein peptide-induced autoimmune prostatitis in the nonobese diabetic mouse. *J Immunol* 179: 1559-1567.
17. Morelli, A., L. Vignozzi, S. Filippi, G. B. Vannelli, S. Ambrosini, R. Mancina, C. Crescioli, S. Donati, B. Fibbi, E. Colli, L. Adorini, and M. Maggi. 2007. BXL-628, a vitamin D receptor agonist effective in benign prostatic hyperplasia treatment, prevents RhoA activation and inhibits RhoA/Rho kinase signaling in rat and human bladder. *Prostate* 67: 234-247.
18. Maehr, H., M. Uskokovic, L. Adorini, G. Penna, R. Mariani, P. Panina, N. Passini, E. Bono, S. Perego, M. Biffi, M. Holick, C. Spina, and N. Suh. 2007. Calcitriol derivatives with two different side chains at C-20 III. An epimeric pair of the gemini family with unprecedented antiproliferative effects on tumor cells and renin mRNA expression inhibition. *J Steroid Biochem Mol Biol* 103: 277-281.
19. Giarratana, N., G. Penna, and L. Adorini. 2007. Animal models of spontaneous autoimmune disease: type 1 diabetes in the nonobese diabetic mouse. *Methods Mol Biol* 380: 285-311.
20. Garay, E., P. Jankowski, P. Lizano, S. Marczak, H. Maehr, L. Adorini, M. R. Uskokovic, and G. P. Studzinski. 2007. Calcitriol derivatives with two different side-chains at C-20. Part 4: further chain modifications that alter VDR-dependent monocytic differentiation potency in human leukemia cells. *Bioorg Med Chem* 15: 4444-4455.
21. Adorini, L., G. Penna, S. Amuchastegui, C. Cossetti, F. Aquilano, R. Mariani, B. Fibbi, A. Morelli, M. Uskokovic, E. Colli, and M. Maggi. 2007. Inhibition of prostate growth and inflammation by the vitamin D receptor agonist BXL-628 (elocalcitol). *J Steroid Biochem Mol Biol* 103: 689-693.
22. Uskokovic, M. R., P. Manchand, S. Marczak, H. Maehr, P. Jankowski, L. Adorini, and G. S. Reddy. 2006. C-20 cyclopropyl vitamin D3 analogs. *Curr Top Med Chem* 6: 1289-1296.

23. Penna, G., S. Amuchastegui, C. Cossetti, F. Aquilano, R. Mariani, F. Sanvito, C. Doglioni, and L. Adorini. 2006. Treatment of experimental autoimmune prostatitis in nonobese diabetic mice by the vitamin D receptor agonist elocalcitol. *J Immunol* 177: 8504-8511.
24. Marchiani, S., L. Bonaccorsi, P. Ferruzzi, C. Crescioli, M. Muratori, L. Adorini, G. Forti, M. Maggi, and E. Baldi. 2006. The vitamin D analogue BXL-628 inhibits growth factor-stimulated proliferation and invasion of DU145 prostate cancer cells. *J Cancer Res Clin Oncol* 132: 408-416.
25. Maggi, M., C. Crescioli, A. Morelli, E. Colli, and L. Adorini. 2006. Pre-clinical evidence and clinical translation of benign prostatic hyperplasia treatment by the vitamin D receptor agonist BXL-628 (Elocalcitol). *J Endocrinol Invest* 29: 665-674.
26. Campbell, M. J., and L. Adorini. 2006. The vitamin D receptor as a therapeutic target. *Expert Opin Ther Targets* 10: 735-748.
27. Adorini, L., K. C. Daniel, and G. Penna. 2006. Vitamin D receptor agonists, cancer and the immune system: an intricate relationship. *Curr Top Med Chem* 6: 1297-1301.
28. Spina, C., V. Tangpricha, M. Yao, W. Zhou, M. M. Wolfe, H. Maehr, M. Uskokovic, L. Adorini, and M. F. Holick. 2005. Colon cancer and solar ultraviolet B radiation and prevention and treatment of colon cancer in mice with vitamin D and its Gemini analogs. *J Steroid Biochem Mol Biol* 97: 111-120.
29. Riboldi, E., T. Musso, E. Moroni, C. Urbinati, S. Bernasconi, M. Rusnati, L. Adorini, M. Presta, and S. Sozzani. 2005. Cutting edge: proangiogenic properties of alternatively activated dendritic cells. *J Immunol* 175: 2788-2792.
30. Penna, G., A. Roncari, S. Amuchastegui, K. C. Daniel, E. Berti, M. Colonna, and L. Adorini. 2005. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4⁺Foxp3⁺ regulatory T cells by 1,25-dihydroxyvitamin D3. *Blood* 106: 3490-3497.
31. Penna, G., N. Giarratana, S. Amuchastegui, R. Mariani, K. C. Daniel, and L. Adorini. 2005. Manipulating dendritic cells to induce regulatory T cells. *Microbes Infect* 7: 1033-1039.
32. Olcott, A. P., J. Tian, V. Walker, H. Dang, B. Middleton, L. Adorini, L. Washburn, and D. L. Kaufman. 2005. Antigen-based therapies using ignored determinants of beta cell antigens can more effectively inhibit late-stage autoimmune disease in diabetes-prone mice. *J Immunol* 175: 1991-1999.
33. Gauzzi, M. C., C. Purificato, K. Donato, Y. Jin, L. Wang, K. C. Daniel, A. A. Maghazachi, F. Belardelli, L. Adorini, and S. Gessani. 2005. Suppressive effect of 1 α ,25-dihydroxyvitamin D3 on type I IFN-mediated monocyte differentiation into dendritic cells: impairment of functional activities and chemotaxis. *J Immunol* 174: 270-276.
34. Gauzzi, M. C., C. Purificato, L. Conti, L. Adorini, F. Belardelli, and S. Gessani. 2005. IRF-4 expression in the human myeloid lineage: up-regulation during dendritic cell differentiation and inhibition by 1 α ,25-dihydroxyvitamin D3. *J Leukoc Biol* 77: 944-947.

35. Del Corno, M., M. C. Gauzzi, G. Penna, F. Belardelli, L. Adorini, and S. Gessani. 2005. Human immunodeficiency virus type 1 gp120 and other activation stimuli are highly effective in triggering alpha interferon and CC chemokine production in circulating plasmacytoid but not myeloid dendritic cells. *J Virol* 79: 12597-12601.
36. Crescioli, C., A. Morelli, L. Adorini, P. Ferruzzi, M. Luconi, G. B. Vannelli, M. Marini, S. Gelmini, B. Fibbi, S. Donati, D. Villari, G. Forti, E. Colli, K. E. Andersson, and M. Maggi. 2005. Human bladder as a novel target for vitamin D receptor ligands. *J Clin Endocrinol Metab* 90: 962-972.
37. Amuchastegui, S., K. C. Daniel, and L. Adorini. 2005. Inhibition of acute and chronic allograft rejection in mouse models by BXL-628, a nonhypercalcemic vitamin D receptor agonist. *Transplantation* 80: 81-87.
38. Adorini, L., S. Amuchastegui, and K. C. Daniel. 2005. Prevention of chronic allograft rejection by Vitamin D receptor agonists. *Immunol Lett* 100: 34-41.
39. Adorini, L. 2005. Intervention in autoimmunity: the potential of vitamin D receptor agonists. *Cell Immunol* 233: 115-124.
40. Ria, F., A. Gallard, C. R. Gabaglia, J. C. Guery, E. E. Sercarz, and L. Adorini. 2004. Selection of similar naive T cell repertoires but induction of distinct T cell responses by native and modified antigen. *J Immunol* 172: 3447-3453.
41. Olivera, C. J., C. M. Bula, J. E. Bishop, L. Adorini, P. Manchand, M. R. Uskokovic, and A. W. Norman. 2004. Characterization of five 19-nor-analogs of 1alpha,25(OH)2-Vitamin D3 with 20-cyclopropyl-modified side-chains: implications for ligand binding and calcemic properties. *J Steroid Biochem Mol Biol* 89-90: 99-106.
42. Maehr, H., M. R. Uskokovic, G. S. Reddy, and L. Adorini. 2004. Calcitriol derivatives with two different side chains at C-20. 24-hydroxy derivatives as metabolic products and molecular probes for VDR exploration. *J Steroid Biochem Mol Biol* 89-90: 35-38.
43. Maehr, H., M. R. Uskokovic, L. Adorini, and G. S. Reddy. 2004. Calcitriol derivatives with two different side chains at C-20. II. Diastereoselective syntheses of the metabolically produced 24(R)-hydroxygemini. *J Med Chem* 47: 6476-6484.
44. Giarratana, N., G. Penna, S. Amuchastegui, R. Mariani, K. C. Daniel, and L. Adorini. 2004. A vitamin D analog down-regulates proinflammatory chemokine production by pancreatic islets inhibiting T cell recruitment and type 1 diabetes development. *J Immunol* 173: 2280-2287.
45. Crescioli, C., P. Ferruzzi, A. Caporali, M. Scaltriti, S. Bettuzzi, R. Mancina, S. Gelmini, M. Serio, D. Villari, G. B. Vannelli, E. Colli, L. Adorini, and M. Maggi. 2004. Inhibition of prostate cell growth by BXL-628, a calcitriol analogue selected for a phase II clinical trial in patients with benign prostate hyperplasia. *Eur J Endocrinol* 150: 591-603.
46. Adorini, L., G. Penna, N. Giarratana, A. Roncari, S. Amuchastegui, K. C. Daniel, and M. Uskokovic. 2004. Dendritic cells as key targets for immunomodulation by Vitamin D receptor ligands. *J Steroid Biochem Mol Biol* 89-90: 437-441.

47. Adorini, L., N. Giarratana, and G. Penna. 2004. Pharmacological induction of tolerogenic dendritic cells and regulatory T cells. *Semin Immunol* 16: 127-134.
48. Adorini, L. 2004. Immunotherapeutic approaches in multiple sclerosis. *J Neurol Sci* 223: 13-24.
49. Adorini, L. 2004. Antigen-based immunointervention in human autoimmune diseases. *Trends Biotechnol* 22: 547-549.
50. Vulcano, M., S. Struyf, P. Scapini, M. Cassatella, S. Bernasconi, R. Bonecchi, A. Calleri, G. Penna, L. Adorini, W. Luini, A. Mantovani, J. Van Damme, and S. Sozzani. 2003. Unique regulation of CCL18 production by maturing dendritic cells. *J Immunol* 170: 3843-3849.
51. Trembleau, S., G. Penna, S. Gregori, N. Giarratana, and L. Adorini. 2003. IL-12 administration accelerates autoimmune diabetes in both wild-type and IFN-gamma-deficient nonobese diabetic mice, revealing pathogenic and protective effects of IL-12-induced IFN-gamma. *J Immunol* 170: 5491-5501.
52. Pozzilli, P., and L. Adorini. 2003. Prevention of type 1 diabetes: where do we start? *J Endocrinol Invest* 26: 292-293.
53. Martinez, N. R., P. Augstein, A. K. Moustakas, G. K. Papadopoulos, S. Gregori, L. Adorini, D. C. Jackson, and L. C. Harrison. 2003. Disabling an integral CTL epitope allows suppression of autoimmune diabetes by intranasal proinsulin peptide. *J Clin Invest* 111: 1365-1371.
54. Gregori, S., N. Giarratana, S. Smiroldo, and L. Adorini. 2003. Dynamics of pathogenic and suppressor T cells in autoimmune diabetes development. *J Immunol* 171: 4040-4047.
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56. Crescioli, C., P. Ferruzzi, A. Caporali, R. Mancina, A. Comerci, M. Muratori, M. Scaltriti, G. B. Vannelli, S. Smiroldo, R. Mariani, D. Villari, S. Bettuzzi, M. Serio, L. Adorini, and M. Maggi. 2003. Inhibition of spontaneous and androgen-induced prostate growth by a nonhypercalcemic calcitriol analog. *Endocrinology* 144: 3046-3057.
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59. Adorini, L. 2003. Tolerogenic dendritic cells induced by vitamin D receptor ligands enhance regulatory T cells inhibiting autoimmune diabetes. *Ann N Y Acad Sci* 987: 258-261.
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61. Polastri, L., F. Galbiati, F. Bertuzzi, P. Fiorina, R. Nano, S. Gregori, L. Aldrichetti, G. Pozza, A. Secchi, L. Adorini, and A. M. Davalli. 2002. Secretory

- defects induced by immunosuppressive agents on human pancreatic beta-cells. *Acta Diabetol* 39: 229-233.
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64. Mazzeo, D., S. Sacco, P. Di Lucia, G. Penna, L. Adorini, P. Panina-Bordignon, and P. Ghezzi. 2002. Thiol antioxidants inhibit the formation of the interleukin-12 heterodimer: a novel mechanism for the inhibition of IL-12 production. *Cytokine* 17: 285-293.
65. Mathieu, C., and L. Adorini. 2002. The coming of age of 1,25-dihydroxyvitamin D(3) analogs as immunomodulatory agents. *Trends Mol Med* 8: 174-179.
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PATENTS

Novel method of treatment of male sub-fertility

Inventor: COLLI ENRICO ; PENNA GIUSEPPE (+1)

Applicant: BIOXELL SPA

EC: A61K31/59; A61K31/593 IPC: A61K31/59; A61K31/593; A61P15/00; (+3)

Publication info: AU2007306292 (A1) — 2008-04-17

20-Alkyl, Gemini Vitamin D3 Compounds and Methods of Use Thereof

Inventor: JANKOWSKI PAWEL [US] USKOKOVIC MILAN R [US] (+1)

Applicant: BIOXELL SPA [IT]

EC: C07C401/00 IPC: A61K31/593; A61P13/00; C07C401/00; (+3)

Publication info: US2009099140 (A1) — 2009-04-16

Treating and/or preventing benign prostatic hypertrophy, using 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol to induce apoptosis in prostate cells

Inventor: ADORINI LUCIANO ; COLLI ENRICO

Applicant: BIOXELL SPA [IT]

EC: A61K31/59; A61K31/59; (+3) IPC: A61K31/59; A61K31/593; A61K45/06; (+7)

Publication info: BRPI0404050 (A) — 2005-06-14

Compound and use for the treatment of benign prostatic hyperplasia and relative diseases

Inventor: ADORINI LUCIANO [IT] ; COLLI ENRICO [IT]

Applicant: BIOXELL SPA [IT]

EC: IPC: A61K31/593; A61P13/08; A61K31/59; (+1)

Publication info: CN101352446 (A) — 2009-01-28

Novel method

Inventor: ADORINI LUCIANO [IT]

Applicant: BIOXELL SPA [IT]

EC: IPC: A61K31/59; A61K31/592; A61P35/00; (+2)

Publication info: CA2646712 (A1) — 2007-10-04

20-Cyclopropyl, 26,27-Alkyl/Haloalkyl Vitamin D3 compounds and methods of use thereof

Inventor: USKOKOVIC MILAN R [US] ; ADORINI LUCIANO [IT] (+3)

Applicant: BIOXELL SPA [IT]

EC: C07C401/00 IPC: C07C401/00; A61K31/593; A61P13/10; (+7)

Publication info: US2008318911 (A1) — 2008-12-25

Combined use of Vitamin D derivatives and anti-proliferative agents for treating bladder cancer

Inventor: ADORINI LUCIANO [IT] ; PENNA GIUSEPPE [IT]

Applicant:

EC: A61K31/59; A61K31/70; (+1) IPC: A61K31/704; A61K31/593; A61P35/00; (+3)
Publication info: US2008293647 (A1) — 2008-11-27

Gemini vitamin D3 compounds and methods of use thereof

Inventor: ADORINI LUCIANO [IT] ; PENNA GIUSEPPE [IT] (+2)

Applicant: BIOXELL SPA [IT]

EC: C07C401/00; A61K9/48H4 IPC: A61K31/593; A61P13/00; A61P35/00; (+7)

Publication info: US2008280859 (A1) — 2008-11-13

Use of a vitamin D3 analogue for the treatment of autoimmune diabetes

Inventor: ADORINI LUCIANO [IT] ; GIARRATANA NADIA [IT] (+3)

Applicant: BIOXELL SPA [IT]

EC: A61K31/593 IPC: A61K31/593; A61P3/10; A61P37/02; (+4)

Publication info: AT410172 (T) — 2008-10-15

Method for treating benign prostatic hyperplasia

Inventor: ADORINI LUCIANO [IT] ; COLLI ENRICO [IT]

Applicant: BIOXELL SPA [IT]

EC: A61K31/593 IPC: A61K31/047; A61K31/593; A61P13/08; (+3)

Publication info: US2008207769 (A1) — 2008-08-28

20-alkyl, gemini vitamin D3 compounds and methods of use thereof

Inventor: PAWEL JANKOWSKI [IT] ; LUCIANO ADORINI [IT]

Applicant: BIOXELL SPA [IT]

EC: A61K31/593 IPC: A61K31/593; C07C401/00; A61K31/59; (+1)

Publication info: CN101198336 (A) — 2008-06-11

1,3 Aclyated 24-keto-vitamin d3 compounds and methods of use thereof

Inventor: ADORINI LUCIANO [IT] ; PENNA GIUSEPPE [IT] (+2)

Applicant: BIOXELL SPA [IT]

EC: C07C401/00 IPC: A61K31/59; A61K31/593; C07C401/00; (+3)

Publication info: US2007032461 (A1) — 2007-02-08

1,3-Diacylated, 26,27-Alkyl/Haloalkyl Vitamin D3 compounds and methods of use thereof

Inventor: USKOKOVIC MILAN R [US] ; ADORINI LUCIANO [IT] (+2)

Applicant: BIOXELL SPA [IT]

EC: C07C401/00 IPC: A61K31/593; A61K31/59; A61P3/10; (+23)

Publication info: US2008064668 (A1) — 2008-03-13

Use of vitamin D compounds for the prevention or treatment of chronic prostatitis

Inventor: ADORINI LUCIANO [IT] ; PENNA GIUSEPPE [IT]

Applicant: BIOXELL SPA [IT] ; ADORINI LUCIANO [IT] (+1)

EC: A61K31/592; A61K31/593 IPC: A61K31/593; A61K31/592; A61P13/08; (+2)
Publication info: WO2006035075 (A1) — 2006-04-06

Gemini vitamin D3 compounds and methods of use thereof

Inventor: ADORINI LUCIANO [IT] ; PENNA GIUSEPPE [IT] (+3)
Applicant: BIOXELL SPA [IT] ; UNIV CHICAGO [US]
EC: C07C401/00 IPC: A01N45/00; C07C1/00; A01N45/00; (+4)
Publication info: EP1622455 (A2) — 2006-02-08

Compound and use in treatment

Inventor: ADORINI LUCIANO [IT] ; COLLI ENRICO [IT]
Applicant: BIOXELL SPA [IT]
EC: A61K31/593 IPC: A61K31/593; A61K31/59; (IPC1-7): A61P13/08; (+1)
Publication info: GB2407499 (A) — 2005-05-04

Use of a vitamin D3 analogue for the treatment of autoimmune diabetes

Inventor: ADORINI LUCIANO [IT] ; GIARRATANA NADIA [IT] (+3)
Applicant: BIOXELL SPA [IT]
EC: IPC: A61K31/593; A61P37/02; A61K31/59; (+2)
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